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SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Khatol Shahnan-Shah Examiner #: 78526 Date: 4/27/03
Art Unit: 1645 Phone Number 30 8-8896 Serial Number: 09/674,935
Mail Box and Bldg/Room Location: 8-D-16 Results Format Preferred (circle): PAPER DISK E-MAIL
8E-12

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Vaccine

Inventors (please provide full names): See bib sheet attached

Earliest Priority Filing Date: 5/8/1998

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search claim 1-37
attached.

Point of Contact:
Toby Port
Technical Info. Specialist
CM1 6A04
703-308-3534

Claims and amended claims
1, 31, 32, 34, are attached
key words are highlighted
Thanks.

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APR 28 2003
TECH CENTER 1600/2900

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STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher:	NA Sequence (#)		STN	355
Searcher Phone #:	AA Sequence (#)		Dialog	
Searcher Location:	Structure (#)		Questel/Orbit	
Date Searcher Picked Up:	4/30	Bibliographic	X	Dr.Link
Date Completed:	5/7	Litigation		Lexis/Nexis
Searcher Prep & Review Time:	30	Fulltext		Sequence Systems
Clerical Prep Time:		Patent Family		WWW/Internet
Online Time:	120	Other		Other (specify)

PTO-1590 (8-01)

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=> file hcaplus
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FILE COVERS 1907 - 7 May 2003  VOL 138 ISS 19
FILE LAST UPDATED: 6 May 2003  (20030506/ED)

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 substance identification.

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L2  (      1196)SEA FILE=HCAPLUS ABB=ON  PLU=ON  IMMUN? (1A) MEMOR?
L3            1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L1 AND L2



L4  (        53)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ETXB
L5  (        68)SEA FILE=HCAPLUS ABB=ON  PLU=ON  LT-R72 OR LTK63 OR LT K63 OR
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L6  (       107)SEA FILE=HCAPLUS ABB=ON  PLU=ON  CTXB
L7  (         1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  VTXB
L8  (     32703)SEA FILE=HCAPLUS ABB=ON  PLU=ON  VACCINES/CT
L9  (     30528)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ?HERPES?
L10           8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L4 OR L5 OR L6 OR L7) AND L8
                AND L9



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L12 (        68)SEA FILE=HCAPLUS ABB=ON  PLU=ON  LT-R72 OR LTK63 OR LT K63 OR
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L14 (         1)SEA FILE=HCAPLUS ABB=ON  PLU=ON  VTXB
L15 (     32703)SEA FILE=HCAPLUS ABB=ON  PLU=ON  VACCINES/CT
L16 (     22790)SEA FILE=HCAPLUS ABB=ON  PLU=ON  HSV? OR EBV? OR VZV? OR CMV?
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L17 (         6)SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L11 OR L12 OR L13 OR L14)
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L18           5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L17 NOT MICROEMULS?/TI



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L20 (        68)SEA FILE=HCAPLUS ABB=ON  PLU=ON  LT-R72 OR LTK63 OR LT K63 OR
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L23 (     31805)SEA FILE=HCAPLUS ABB=ON  PLU=ON  IMMUNOMODULATORS+NT/CT
L24 (     30528)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ?HERPES?
L25           8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L19 OR L20 OR L21 OR L22)
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L26 (        53)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ETXB
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L28 (       107)SEA FILE=HCAPLUS ABB=ON  PLU=ON  CTXB
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L30 (     31805)SEA FILE=HCAPLUS ABB=ON  PLU=ON  IMMUNOMODULATORS+NT/CT
L31 (     22790)SEA FILE=HCAPLUS ABB=ON  PLU=ON  HSV? OR EBV? OR VZV? OR CMV?
                OR HHV?
L32           5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L26 OR L27 OR L28 OR L29)
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L34 (     32703)SEA FILE=HCAPLUS ABB=ON  PLU=ON  VACCINES/CT
L35 (     31805)SEA FILE=HCAPLUS ABB=ON  PLU=ON  IMMUNOMODULATORS+NT/CT
L36 (        30)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33 AND L34
L37 (        21)SEA FILE=HCAPLUS ABB=ON  PLU=ON  L33 AND L35
L38 (     30528)SEA FILE=HCAPLUS ABB=ON  PLU=ON  ?HERPES?
L39 (     22790)SEA FILE=HCAPLUS ABB=ON  PLU=ON  HSV? OR EBV? OR VZV? OR CMV?
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L40           3 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L36 OR L37) AND (L38 OR L39)


=> s l3 or l10 or l18 or l25 or l32 or l40
L92          11 L3 OR L10 OR L18 OR L25 OR L32 OR L40

=> file medline; d que l47; d que l53; d que l55
FILE 'MEDLINE' ENTERED AT 12:56:02 ON 07 MAY 2003

 FILE LAST UPDATED: 6 MAY 2003 (20030506/UP). FILE COVERS 1958 TO DATE.

 On April 13, 2003, MEDLINE was reloaded. See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2003 vocabulary. See http://www.nlm.nih.gov/mesh/changes2003.html
 for a description on changes.

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L41 (       895)SEA FILE=MEDLINE ABB=ON  PLU=ON  EXTB OR ENTEROTOXIN LT/CN
L42 (        76)SEA FILE=MEDLINE ABB=ON  PLU=ON  CTXB OR VTXB
L43 (      6161)SEA FILE=MEDLINE ABB=ON  PLU=ON  IMMUNOLOGIC MEMORY/CT
L44 (     98562)SEA FILE=MEDLINE ABB=ON  PLU=ON  ADJUVANTS, IMMUNOLOGIC+NT/CT
L45 (     86912)SEA FILE=MEDLINE ABB=ON  PLU=ON  VACCINES+NT/CT
L46 (     39422)SEA FILE=MEDLINE ABB=ON  PLU=ON  HERPESVIR?
L47           4 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L41 OR L42) AND (L43 OR L44
                OR L45) AND L46
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L48 (       227)SEA FILE=MEDLINE ABB=ON  PLU=ON  (GM1 OR GM 1 OR GB3 OR GB 3)
                (2A) BINDING
L49 (      6161)SEA FILE=MEDLINE ABB=ON  PLU=ON  IMMUNOLOGIC MEMORY/CT
L50 (     98562)SEA FILE=MEDLINE ABB=ON  PLU=ON  ADJUVANTS, IMMUNOLOGIC+NT/CT
L51 (     86912)SEA FILE=MEDLINE ABB=ON  PLU=ON  VACCINES+NT/CT
L52 (     39422)SEA FILE=MEDLINE ABB=ON  PLU=ON  HERPESVIR?
L53           0 SEA FILE=MEDLINE ABB=ON  PLU=ON  L48 AND (L49 OR L50 OR L51)
                AND L52


L43 (      6161)SEA FILE=MEDLINE ABB=ON  PLU=ON  IMMUNOLOGIC MEMORY/CT
L44 (     98562)SEA FILE=MEDLINE ABB=ON  PLU=ON  ADJUVANTS, IMMUNOLOGIC+NT/CT
L45 (     86912)SEA FILE=MEDLINE ABB=ON  PLU=ON  VACCINES+NT/CT
L46 (     39422)SEA FILE=MEDLINE ABB=ON  PLU=ON  HERPESVIR?
L55           0 SEA FILE=MEDLINE ABB=ON  PLU=ON  ETXB AND (L43 OR L44 OR L45)
                AND L46

=> file embase; d que l64; d que l69
FILE 'EMBASE' ENTERED AT 12:56:20 ON 07 MAY 2003
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 FILE COVERS 1974 TO 1 May 2003 (20030501/ED)

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 This file contains CAS Registry Numbers for easy and accurate
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L64       42652 SEA FILE=EMBASE ABB=ON  PLU=ON  HERPES



L56          90 SEA FILE=EMBASE ABB=ON  PLU=ON  ETXB OR CTXB OR VTXB
L58        3888 SEA FILE=EMBASE ABB=ON  PLU=ON  IMMUNOMODULATING AGENT/CT
L59        1094 SEA FILE=EMBASE ABB=ON  PLU=ON  IMMUNOSTIMULATING AGENT/CT
L60       18674 SEA FILE=EMBASE ABB=ON  PLU=ON  IMMUNOSUPPRESSIVE AGENT/CT
L61        1435 SEA FILE=EMBASE ABB=ON  PLU=ON  IMMUNOLOGICAL MEMORY/CT
L62        1627 SEA FILE=EMBASE ABB=ON  PLU=ON  IMMUNOLOGICAL ADJUVANT/CT
L63       75173 SEA FILE=EMBASE ABB=ON  PLU=ON  VACCINE+NT/CT
L69           5 SEA FILE=EMBASE ABB=ON  PLU=ON  L56 AND (L58 OR L59 OR L60 OR
                L61 OR L62 OR L63) AND MUCOS?


=> file biosis; d que l76; d que l80; d que l83
FILE 'BIOSIS' ENTERED AT 12:56:37 ON 07 MAY 2003
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 30 April 2003 (20030430/ED)
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L70          70 SEA FILE=BIOSIS ABB=ON  PLU=ON  ETXB OR CTSB OR VTXB
L71         101 SEA FILE=BIOSIS ABB=ON  PLU=ON  (GM1 OR GM 1 OR GB 3 OR GB3)
                (W) (BINDING)
L74       94247 SEA FILE=BIOSIS ABB=ON  PLU=ON  HERPES?
L75       37335 SEA FILE=BIOSIS ABB=ON  PLU=ON  HSV OR EBV? OR CMV? OR HHV? OR
                VZV?
L76           6 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L70 OR L71) AND (L74 OR L75)


L70          70 SEA FILE=BIOSIS ABB=ON  PLU=ON  ETXB OR CTSB OR VTXB
L71         101 SEA FILE=BIOSIS ABB=ON  PLU=ON  (GM1 OR GM 1 OR GB 3 OR GB3)
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L72      106613 SEA FILE=BIOSIS ABB=ON  PLU=ON  VACCIN?
L77      108226 SEA FILE=BIOSIS ABB=ON  PLU=ON  MUCOS?
L79          10 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L70 OR L71) AND L72 AND L77
L80           3 SEA FILE=BIOSIS ABB=ON  PLU=ON  L79 AND (AFFINITY OR PEYER? OR
                PERTUSSIS)/TI


L70          70 SEA FILE=BIOSIS ABB=ON  PLU=ON  ETXB OR CTSB OR VTXB
L71         101 SEA FILE=BIOSIS ABB=ON  PLU=ON  (GM1 OR GM 1 OR GB 3 OR GB3)
                (W) (BINDING)
L81      156175 SEA FILE=BIOSIS ABB=ON  PLU=ON  INFLUENZ? OR PNEUMO? OR
                MENINGIT?
L82       97183 SEA FILE=BIOSIS ABB=ON  PLU=ON  HEPATIT?
L83           5 SEA FILE=BIOSIS ABB=ON  PLU=ON  (L70 OR L71) AND (L81 OR L82)


=> s l76 or l80 or l83
L93          14 L76 OR L80 OR L83

=> file wpid; d que l89; d que l91
FILE 'WPIDS' ENTERED AT 12:57:02 ON 07 MAY 2003
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FILE LAST UPDATED:          5 MAY 2003      <20030505/UP>
MOST RECENT DERWENT UPDATE:     200329        <200329/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

    Due to data production problems in updates 24 and 25
    the WPI file had to be reset to update 200323 on April 24
    and the corrected updates were reloaded.
    SDIs for update 24 were rerun. The previous SDI run for 24 has
    been credited.
    We also recommend to recreate answer sets dated between April 10
    and 24.  Charges incurred to accomplish this will be credited of
    course.

>>> NEW WEEKLY SDI FREQUENCY AVAILABLE --> see NEWS  <<<

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY <<<

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
    SEE http://www.derwent.com/dwpi/updates/dwpicov/index.html <<<

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE,
    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<
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>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://www.derwent.com/userguides/dwpi_guide.html <<<


L84          31 SEA FILE=WPIDS ABB=ON  PLU=ON  ETXB OR CTXB OR VTXB OR
                ENTEROTOXIN LT
L85           9 SEA FILE=WPIDS ABB=ON  PLU=ON  (GM1 OR GM 1 OR GB3 OR GB 3)
                (W) BINDING
L86       66064 SEA FILE=WPIDS ABB=ON  PLU=ON  VACCIN? OR IMMUNO?
L88           8 SEA FILE=WPIDS ABB=ON  PLU=ON  (L84 OR L85) AND L86 AND MUCOS?

L89           6 SEA FILE=WPIDS ABB=ON  PLU=ON  L88 NOT CONTRACEPT?/TI



L84          31 SEA FILE=WPIDS ABB=ON  PLU=ON  ETXB OR CTXB OR VTXB OR
                ENTEROTOXIN LT
L85           9 SEA FILE=WPIDS ABB=ON  PLU=ON  (GM1 OR GM 1 OR GB3 OR GB 3)
                (W) BINDING
L86       66064 SEA FILE=WPIDS ABB=ON  PLU=ON  VACCIN? OR IMMUNO?
L90      143064 SEA FILE=WPIDS ABB=ON  PLU=ON  HERPES? OR HSV? OR EBV OR VZV
                OR HHV? OR INFLUENZ? OR MENINGIT? OR PNEUM? OR HEPATIT? OR
                RESPIRAT?
L91          10 SEA FILE=WPIDS ABB=ON  PLU=ON  (L84 OR L85) AND L86 AND L90


=> s l89 or l91
L94          13 L89 OR L91

=> dup rem l47 l92 l69 l93 l94
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FILE 'WPIDS' ENTERED AT 12:59:57 ON 07 MAY 2003
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PROCESSING COMPLETED FOR L47
PROCESSING COMPLETED FOR L92
PROCESSING COMPLETED FOR L69
PROCESSING COMPLETED FOR L93
PROCESSING COMPLETED FOR L94
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                ANSWERS '5-14' FROM FILE HCAPLUS
                ANSWERS '15-19' FROM FILE EMBASE
                ANSWERS '20-32' FROM FILE BIOSIS
                ANSWERS '33-43' FROM FILE WPIDS

=> d ibib ab l95 1-43

L95  ANSWER 1 OF 43     MEDLINE                      DUPLICATE 3
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ACCESSION NUMBER: 2001192726 MEDLINE
DOCUMENT NUMBER: 21105201 PubMed ID: 11160664
TITLE: Protective mucosal immunity to ocular herpes simplex virus type 1 infection in mice by using Escherichia coli heat-labile enterotoxin B subunit as an adjuvant.
AUTHOR: Richards C M; Aman A T; Hirst T R; Hill T J; Williams N A
CORPORATE SOURCE: Department of Pathology and Microbiology, School of Medical Sciences, University of Bristol, Bristol BS8 1TD, United Kingdom.. Claire.M.Richards@bristol.ac.uk
SOURCE: JOURNAL OF VIROLOGY, (2001 Feb) 75 (4) 1664-71.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010410
Last Updated on STN: 20010410
Entered Medline: 20010405

AB The potential of nontoxic recombinant B subunits of cholera toxin (rCtxB) and its close relative Escherichia coli heat-labile enterotoxin (rEtxB) to act as mucosal adjuvants for intranasal immunization with herpes simplex virus type 1 (HSV-1) glycoproteins was assessed. Doses of 10 microg of rEtxB or above with 10 microg of HSV-1 glycoproteins elicited high serum and mucosal anti-HSV-1 titers comparable with that obtained using **CtxB** (10 microg) with a trace (0.5 microg) of whole toxin (Ctx-**CtxB**). By contrast, doses of rCtxB up to 100 microg elicited only meager anti-HSV-1 responses. As for Ctx-**CtxB**, rEtxB resulted in a Th2-biased immune response with high immunoglobulin G1 (IgG1)/IgG2a antibody ratios and production of interleukin 4 (IL-4) and IL-10 as well as gamma interferon by proliferating T cells. The protective efficacy of the immune response induced using rEtxB as an adjuvant was assessed following ocular challenge of immunized and mock-immunized mice. Epithelial disease was observed in both groups, but the immunized mice recovered by day 6 whereas mock-immunized mice developed more severe corneal disease leading to stromal keratitis. In addition, a significant reduction in the incidence of lid disease and zosteriform spread was observed in immunized animals and there was no encephalitis compared with 95% encephalitis in mock-immunized mice. The potential of such mucosal adjuvants for use in human vaccines against pathogens such as HSV-1 is discussed.

L95 ANSWER 2 OF 43 MEDLINE
ACCESSION NUMBER: 2003019179 MEDLINE
DOCUMENT NUMBER: 22413645 PubMed ID: 12526058
TITLE: Induction of cellular immunity to varicella-zoster virus glycoproteins tested with pernasal coadministration of Escherichia coli enterotoxin in mice.
AUTHOR: Tsuji Takao; Shiraki Kimiyasu; Sato Hitoshi; Sasaki Keiko; Arita Michiko; Kato Michio; Takahashi Tsuyoshi; Ochi Sadayuki; Ichinose Yoshio; Yokochi Takashi; Asano Yoshizo
CORPORATE SOURCE: Department of Microbiology, School of Medicine, Fujita Health University, Toyoake, Aichi, Japan.. ttsuji@fujita-hu.ac.jp
SOURCE: JOURNAL OF MEDICAL VIROLOGY, (2003 Mar) 69 (3) 451-8.
Journal code: 7705876. ISSN: 0146-6615.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200303

ENTRY DATE: Entered STN: 20030115
Last Updated on STN: 20030401
Entered Medline: 20030331

AB A mutant of Escherichia coli enterotoxin promotes the induction of cellular immunity to a live varicella vaccine (the Oka strain) as a mucosal adjuvant in mice. An investigation was carried out to determine which of the purified glycoproteins of the virus among three induced cellular immunity with a single nasal administration. Spleen cells from mice immunized nasally with the vaccine and toxin produced interleukin-2 (IL-2) at the same level on restimulation in vitro with glycoprotein H: glycoprotein L (gH:gL), gB, and gE:gI, but not IL-4. The spleen cells from mice immunized with gH:gL, gB, or gE:gI and toxin produced IL-2 on restimulation with gH:gL, gB, or gE:gI, respectively, and the vaccine, but not IL-4. Immunization with gH:gL and the toxin showed increased thymidine uptake and production of IL-2 and interferon-gamma (IFN-gamma) of the spleen cells, but not IL-4, depending on the dose of gH:gL used for immunization and restimulation in vitro. Purified gE:gI and gB have been reported to be the strongest stimulators of cellular immunity to varicella upon subcutaneous injection and are useful as a subunit vaccine. All the glycoproteins tested are excellent stimulators of cellular immunity to the virus and itself on nasal co-immunization with the toxin.

L95 ANSWER 3 OF 43 MEDLINE
ACCESSION NUMBER: 2000173784 MEDLINE
DOCUMENT NUMBER: 20173784 PubMed ID: 10706968
TITLE: Humoral immunoresponse to varicella-zoster virus pernasally coadministered with Escherichia coli enterotoxin in mice.
AUTHOR: Tsuji T; Shiraki K; Sato H; Yue-Mea J; Honma Y; Yoshikawa T; Asano Y
CORPORATE SOURCE: Department of Microbiology, Fujita Health University, School of Medicine, Toyoake, Aichi, Japan.
SOURCE: VACCINE, (2000 Apr 3) 18 (19) 2049-54.
Journal code: 8406899. ISSN: 0264-410X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000518
Last Updated on STN: 20000518
Entered Medline: 20000508

AB It is evaluated whether Escherichia coli enterotoxin is useful for induction of immunity to varicella-zoster virus (VZV) as a mucosal adjuvant in mice. When a commercially available live varicella vaccine (Oka strain) and toxin were administered simultaneously via a nasal route three times at 2 or 6 month intervals, an antibody neutralizing VZV was detected in half or all of the mice vaccinated, respectively. The antibody specific to the vaccine strain of VZV reacted to five proteins, molecular weights of which were 110 K, 100 K, 62 K, 54 K and 46 K. These proteins were composed of glycosylated products of all kinds of glycoproteins. These results suggest that although a nasal administration of the vaccine without the adjuvant has little immunogenicity in mice, the simultaneous administration of the live vaccine and the toxin over a long period induces a specific humoral immunity to VZV.

L95 ANSWER 4 OF 43 MEDLINE
ACCESSION NUMBER: 2001113004 MEDLINE
DOCUMENT NUMBER: 20567992 PubMed ID: 11115718
TITLE: Adjuvant action of Escherichia coli enterotoxin for delayed-type hypersensitivity to Oka vaccine virus on

pernasal co-administration in mice.
AUTHOR: Sasaki K; Asano Y; Honma Y; Kamiya N; Handa T; Ichinose Y; Yokochi T; Shiraki K; Tsuji T
CORPORATE SOURCE: Department of Microbiology, Fujita Health University, School of Medicine, Toyoake, 470-1192, Aichi, Japan.
SOURCE: VACCINE, (2000 Nov 22) 19 (7-8) 931-6.
Journal code: 8406899. ISSN: 0264-410X.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010208

AB The usefulness of a mutant of Escherichia coli enterotoxin for the induction of cellular immunity to varicella-zoster virus as a mucosal adjuvant is assessed in mice. When a commercially available live varicella vaccine (the Oka strain) and toxin were once administered simultaneously via the nasal route, delayed-type hypersensitivity to Oka vaccine virus was significantly induced and detected by footpad test in mice. Moreover, when spleen cells from mice immunized with the vaccine and toxin were re-stimulated with live vaccine in vitro, they showed more thymidine uptake and produced more IL-2 than those from mice immunized with the vaccine alone. These results suggest that mutant enterotoxin has adjuvant action to induce a specific delayed-type hypersensitivity to Oka vaccine virus on nasal co-administration with live vaccine virus.

L95 ANSWER 5 OF 43 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
ACCESSION NUMBER: 2003:6139 HCAPLUS
DOCUMENT NUMBER: 138:68275
TITLE: Mutant forms of enterotoxin (**EtxB**) and cholera toxin (**CtxB**), and their therapeutic uses as target site-specific carriers
INVENTOR(S): Hirst, Timothy Raymond
PATENT ASSIGNEE(S): University of Bristol, UK
SOURCE: PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003000899	A1	20030103	WO 2002-GB2829	20020620

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2001-15382 A 20010622
AB The present invention describes the use of a mutant form of enterotoxin subunit B (**EtxB**) or cholera toxin subunit B (**CtxB**) to deliver an agent to a target cell wherein the mutant has **GM-1 binding** activity, and a reduced immunogenic and

immunomodulatory activity relative to the wild type form of **EtxB** or **CtxB**. Specifically, the mutant **CtxB** with His to Ala substitution at position 57 is severely defective as an immunomodulator, and the holotoxin exhibits ablated toxicity, and retains the ability to bind with high affinity to GM-1. The invention further discloses that **EtxB** or an **EtxB**(H57A) are able to act as trafficking mols. that facilitates delivery of exogenous epitopes into the endogenous pathway of class I antigen processing and presentation.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L95 ANSWER 6 OF 43 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 2
ACCESSION NUMBER: 2002:415206 HCAPLUS
DOCUMENT NUMBER: 138:142322
TITLE: Enhanced delivery of exogenous peptides into the class I antigen processing and presentation pathway
AUTHOR(S): de Haan, Lolke; Hearn, Arron R.; Rivett, A. Jennifer; Hirst, Timothy R.
CORPORATE SOURCE: Departments of Pathology & Microbiology, School of Medical Sciences, University of Bristol, Bristol, BS8 1TD, UK
SOURCE: Infection and Immunity (2002), 70(6), 3249-3258
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Current immunization strategies, using peptide or protein antigens, generally fail to elicit cytotoxic-T-lymphocyte responses, since these antigens are unable to access intracellular compartments where loading of major histocompatibility complex class I (MHC-I) mols. occurs. In an attempt to circumvent this, we investigated whether the **GM1** receptor-**binding** B subunit of Escherichia coli heat-labile toxin (**EtxB**) could be used to deliver class I epitopes. When a class I epitope was conjugated to **EtxB**, it was delivered into the MHC-I presentation pathway in a **GM1-binding**-dependent fashion and resulted in the appearance of MHC-I-epitope complexes at the cell surface. Importantly, we show that the efficiency of **EtxB** -mediated epitope delivery could be strikingly enhanced by incorporating, adjacent to the class I epitope, a 10-amino-acid segment from the C terminus of the DNA polymerase (Pol) of **herpes** simplex virus. The replacement of this 10-amino-acid segment by a heterologous sequence or the introduction of specific amino acid substitutions within this segment either abolished or markedly reduced the efficiency of class I epitope delivery. If the epitope was extended at its C terminus, **EtxB**-mediated delivery into the class I presentation pathway was found to be completely dependent on proteasome activity. Thus, by combining the GM1-targeting function of **EtxB** with the 10-amino-acid Pol segment, highly efficient delivery of exogenous epitopes into the endogenous pathway of class I antigen processing and presentation can be achieved.

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L95 ANSWER 7 OF 43 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 4
ACCESSION NUMBER: 1999:736498 HCAPLUS
DOCUMENT NUMBER: 131:335799
TITLE: Immunomodulatory activity of B subunits of cholera toxin, verotoxin, and heat-labile enterotoxin
INVENTOR(S): Hirst, Timothy Raymond; Williams, Neil Andrew
PATENT ASSIGNEE(S): University of Bristol, UK
SOURCE: PCT Int. Appl., 63 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958145	A2	19991118	WO 1999-GB1461	19990510
WO 9958145	A3	20000203		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2331832	AA	19991118	CA 1999-2331832	19990510
AU 9939394	A1	19991129	AU 1999-39394	19990510
BR 9910305	A	20010109	BR 1999-10305	19990510
EP 1075274	A2	20010214	EP 1999-922284	19990510
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
GB 2353472	A1	20010228	GB 2000-27072	19990510
JP 2002514607	T2	20020521	JP 2000-547996	19990510
NO 2000005599	A	20010108	NO 2000-5599	20001106

PRIORITY APPLN. INFO.:
GB 1998-9958 A 19980508
GB 1998-11954 A 19980603
GB 1998-12316 A 19980608
WO 1999-GB1461 W 19990510

AB The authors disclose the use of: (i) heat-labile enterotoxin B subunit (**EtxB**), cholera toxin B subunit (**CtxB**) or verotoxin B subunit (**VtxB**) in vaccine prepns. to alter the immune response to pathogens. In one example, the secretory IgA response to **herpes** virus glycoproteins is enhanced by the adjuvant activity of **EtxB**. In addn., the authors disclose the use of agents other than **EtxB** or **CtxB**, which have ganglioside **GM1**-**binding** activity, or an agent other than **VtxB** which has globotriosylceramide (**Gb3**)-**binding** activity for affecting intracellular signaling events.

L95 ANSWER 8 OF 43 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:283809 HCAPLUS
DOCUMENT NUMBER: 134:309691
TITLE: Method of obtaining cellular immune responses from proteins
INVENTOR(S): O'Hagan, Derek; Singh, Manmohan
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001026681	A2	20010419	WO 2000-US28040	20001010
WO 2001026681	A3	20020131		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1221968	A2	20020717	EP 2000-968937	20001010
US 6534064	B1	20030318	US 2000-686345	20001010
JP 2003511420	T2	20030325	JP 2001-529742	20001010

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL

PRIORITY APPLN. INFO.:	US 1999-159298P	P 19991013
	WO 2000-US28040	W 20001010

AB A method for producing a cellular immune response (e.g. cytotoxic T lymphocyte response) in a vertebrate subject comprising administering to the vertebrate subject a vaccine compn. comprising a protein particle antigen and a pharmaceutically acceptable excipient is disclosed. The protein particle antigen is formed from protein derived from a virus, fungus, bacterium, bird or mammal, e.g. **herpes** simplex virus type 2 glycoprotein B, hepatitis C virus core protein, or a HIV envelop protein.

L95 ANSWER 9 OF 43 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:12649 HCAPLUS
DOCUMENT NUMBER: 134:99566
TITLE: Vaccine delivery system using Vibrio cholerae bacteria expressing heterologous antigens
INVENTOR(S): Pizza, Mariagrazia
PATENT ASSIGNEE(S): Chiron S.P.A., Italy
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001000857	A1	20010104	WO 2000-IB974	20000623

W: CA, JP, US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

EP 1194576	A1	20020410	EP 2000-942323	20000623
JP 2003503066	T2	20030128	JP 2001-506849	20000623

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.:	GB 1999-14960	A 19990625
	WO 2000-IB974	W 20000623

AB The invention relates to delivery systems for heterologous antigens. Chromosomal loci within rRNA operons such as those of the 16S or the 23S genes have been identified as useful sites for the integration of nucleic acids into the chromosome of Vibrio cholerae bacteria. A particularly useful regulatory sequence for the direction of high level expression of heterologous antigens in this bacterium has been identified as the OmpU promoter.
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L95 ANSWER 10 OF 43 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:608550 HCAPLUS
DOCUMENT NUMBER: 133:213150
TITLE: Microemulsions with adsorbed macromolecules and microparticles for stimulation of immunity
INVENTOR(S): O'Hagan, Derek; Ott, Gary S.; Donnelly, John; Kazzaz, Jina; Ugozzoli, Mildred; Singh, Manmohan; Barackman, John
PATENT ASSIGNEE(S): Chiron Corp., USA
SOURCE: PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000050006	A2	20000831	WO 2000-US3331	20000209
WO 2000050006	A3	20010118		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1156781	A2	20011128	EP 2000-907228	20000209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002537102	T2	20021105	JP 2000-600618	20000209

PRIORITY APPLN. INFO.:
US 1999-121858P P 19990226
US 1999-146391P P 19990729
US 1999-161997P P 19991028
WO 2000-US3331 W 20000209

AB Microparticles with adsorbent surfaces, methods of making such microparticles, and uses thereof, are disclosed. The microparticles comprise a polymer, such as a poly(.alpha.-hydroxy acid), a polyhydroxy butyric acid, a polycaprolactone, a polyorthoester, a polyanhydride, and the like, and are formed using cationic, anionic, or nonionic detergents. The surface of the microparticles efficiently adsorb biol. active macromols., such as DNA, polypeptides, antigens, and adjuvants. Also provided are compns. of an oil droplet emulsion having a metabolizable oil and an emulsifying agent. Immunogenic compns. having an immunostimulating amt. of an antigenic substance, and an immunostimulating amt. of an adjuvant compn. are also provided. Methods of stimulating an immune response, methods of immunizing a host animal against a viral, bacterial, or parasitic infection, and methods of increasing a Th1 immune response in a host animal by administering to the animal an immunogenic compn. of the microparticles, and/or microemulsions of the invention, are also provided.

L95 ANSWER 11 OF 43 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:363028 HCAPLUS
DOCUMENT NUMBER: 131:168965
TITLE: Intranasal immunization with recombinant gD2 reduces disease severity and mortality following genital challenge with **herpes** simplex virus type 2 in guinea pigs
AUTHOR(S): O'Hagan, Derek; Goldbeck, Cheryl; Ugozzoli, Mildred;

Ott, Gary; Burke, Rae Lyn
CORPORATE SOURCE: Chiron Corporation, Emeryville, CA, 94608, USA
SOURCE: Vaccine (1999), 17(18), 2229-2236
CODEN: VACCDE; ISSN: 0264-410X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The ability of a genetically detoxified mutant of heat labile enterotoxin (**LTK63**) to act as a mucosal adjuvant following intranasal immunization with recombinant gD2 has previously been reported in mice. In the current studies, these observations were extended to the guinea pig model. Immunized guinea pigs were subsequently challenged intravaginally with **HSV**-2. Intranasal immunization with gD2 and **LTK63** induced a significant redn. in disease severity and a redn. in mortality. However, only i.m. immunization with a potent adjuvant (MF59) induced protection against the incidence of disease.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L95 ANSWER 12 OF 43 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:672490 HCAPLUS
DOCUMENT NUMBER: 129:289177
TITLE: Detoxified mutants of bacterial ADP-ribosylating toxins as parenteral adjuvants
INVENTOR(S): Barchfeld, Gail; Del Giudice, Giuseppe; Rappuoli, Rino
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9842375	A1	19981001	WO 1998-US5454	19980319
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9865713	A1	19981020	AU 1998-65713	19980319
AU 741902	B2	20011213		
EP 971738	A1	20000119	EP 1998-911861	19980319
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NZ 500159	A	20001124	NZ 1997-500159	19980319
JP 2001517233	T2	20011002	JP 1998-543271	19980319

PRIORITY APPLN. INFO.: US 1997-41227P P 19970321
US 1998-44696 A 19980318
WO 1998-US5454 W 19980319

AB The present invention provides parenteral adjuvants comprising detoxified mutants of bacterial ADP-ribosylating toxins, esp. pertussis toxin (PT), cholera toxin (CT), and Escherichia coli-derived heat-labile toxin (LT). The immune adjuvant includes **LT-K63**, **LT-R72**, CT-S109 and PT-K9/G129. **LT-K63** was prepd. as parenteral adjuvant for vaccine comprising **herpes** simplex virus type 2 gD antigen, influenza hemagglutinin, and HIV p24 gag.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L95 ANSWER 13 OF 43 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:244025 HCAPLUS
DOCUMENT NUMBER: 129:26743
TITLE: Intranasal immunization of mice with **herpes** simplex virus type 2 recombinant gD2: the effect of adjuvants on mucosal and serum antibody responses
AUTHOR(S): Ugozzoli, M.; O'Hagan, D. T.; Ott, G. S.
CORPORATE SOURCE: Chiron Vaccines, Emeryville, CA, USA
SOURCE: Immunology (1998), 93(4), 563-571
CODEN: IMMUAM; ISSN: 0019-2805
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mucosal immunization offers the potential for inducing IgA antibody responses in the vagina, the site of infection for many viruses, including **herpes** simplex type 2 (**HSV**-2). To investigate this possibility, mice were immunized intranasally with 10 .mu.g glycoprotein D2 (gD2) from **HSV** combined with a series of adjuvants of proven efficacy; the oil in water emulsion MF59, poly(D,L-lactide-co-glycolide) microparticles (PLG) (encapsulated or co-administered), immune-stimulating complexes (iscoms) (incorporated or co-administered with iscomatrix) and the genetically detoxified enterotoxin from Escherichia coli, **LT -K63**. Encapsulation of gD2 into PLG microparticles, incorporation of gD2 into iscoms and co-administration of gD2 with **LT-K63** induced mucosal IgA antibody responses (nasal wash, saliva and vaginal wash) which were greater than those induced by i.m. administration of gD2 with MF59. Intranasal immunization with these formulations also induced substantial levels of serum IgG and neutralizing antibodies. These studies demonstrated that intranasal immunization with potent adjuvants is an effective means to induce mucosal antibody responses, even in the lower genital tract.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L95 ANSWER 14 OF 43 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:115168 HCAPLUS
DOCUMENT NUMBER: 128:221479
TITLE: Recent advances in vaccine adjuvants for systemic and mucosal administration
AUTHOR(S): O'hagan, Derek T.
CORPORATE SOURCE: Chiron Corporation, Emeryville, CA, 947608, USA
SOURCE: Journal of Pharmacy and Pharmacology (1998), 50(1), 1-10
CODEN: JPPMAB; ISSN: 0022-3573
PUBLISHER: Royal Pharmaceutical Society of Great Britain
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with many refs. Although vaccines produced by recombinant DNA technol. are safer than traditional vaccines, which are based on attenuated or inactivated bacteria or viruses, they are often poorly immunogenic. Therefore, adjuvants are often required to enhance the immunogenicity of these vaccines. A no. of adjuvants which are particulates of defined dimensions (< 5 .mu.m) have been shown to be effective in enhancing the immunogenicity of weak antigens in animal models. Two novel adjuvants which possess significant potential for the development of new vaccines include an oil-in-water microemulsion (MF59) and polymeric microparticles. MF59 has been shown to be a potent and safe adjuvant in human subjects with several vaccines (for example **HSV**

-2, HIV-1 and influenza virus). An MF59 adjuvanted influenza has been recommended for approval in Italy. Microparticles prepd. from the biodegradable polymers the poly(lactide-glycolides) (PLG) are currently undergoing extensive pre-clin. evaluation as vaccine adjuvants. Because of their controlled-release characteristics, microparticles also possess considerable potential for the development of single dose vaccines. The development of single dose vaccines would offer significant advantages and would improve vaccination uptake rates in at risk populations, particularly in the developing world. In addn. to systemic administration, microparticles have also also been shown to enhance the immunogenicity of vaccines when administered by mucosal routes. Therefore microparticles may allow the development of novel vaccines which can be administered by non-parenteral routes. Mucosal administration of vaccines would significantly improve patient compliance by allowing immunization to be achieved without the use of needles. An alternative approach to the development of mucosally administered vaccines involves the prodn. of genetically detoxified toxins. Heat labile enterotoxin (LT) from Escherichia coli and cholera toxin from Vibrio cholerae are two closely related bacterially produced toxins, which are the most potent adjuvants available. However, these mols. are too toxic to be used in the development of human vaccines. Nevertheless, these toxins have been modified by site-directed mutagenesis to produce mols. which are adjuvant active, but non-toxic. The most advanced of these mols. (**LTK63**), which has a single amino acid substitution in the enzymically active subunit of LT, is active as an adjuvant, but non-toxic in pre-clin. models. The approach of genetically detoxifying bacterial toxins to produce novel adjuvants offers significant potential for the future development of mucosally administered vaccines.

L95 ANSWER 15 OF 43 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2003133653 EMBASE
TITLE: **Mucosal** immunization with a genetically engineered pertussis toxin S1 fragment-cholera toxin subunit B chimeric protein.
AUTHOR: Lee S.F.; Halperin S.A.; Salloum D.F.; MacMillan A.; Morris A.
CORPORATE SOURCE: S.F. Lee, Department of Applied Oral Sciences, Faculty of Dentistry, Dalhousie University, Halifax, NS, B3H 3J5, Canada. song.lee@dal.ca
SOURCE: Infection and Immunity, (1 Apr 2003) 71/4 (2272-2275). Refs: 18
ISSN: 0019-9567 CODEN: INFIBR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A chimeric protein consisting of a divalent pertussis toxin (PT) S1 fragment linked to the cholera toxin (Ctx) A(2)B fragment was constructed. The chimera induced a **mucosal** immunoglobulin A (IgA) and a serum IgG immune response to PT and **CtxB** in BALB/c mice following intranasal immunization. The immune sera neutralized PT in vitro. In the mouse model of Bordetella pertussis respiratory infection, the chimera-immunized animals showed a significant reduction in bacterial lung counts ($P = 0.01$) from that of the sham control group. Thus, a divalent S1 fragment CtxA2B chimera is an immunogenic antigen and can elicit a protective immunity.

L95 ANSWER 16 OF 43 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002200412 EMBASE

TITLE: Comparison of **mucosal** and systemic humoral immune responses after transcutaneous and oral immunization strategies.
AUTHOR: John M.; Bridges E.A.; Miller A.O.; Calderwood S.B.; Ryan E.T.
CORPORATE SOURCE: E.T. Ryan, Tropical/Geographic Medicine Center, Division of Infectious Diseases, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114, United States. etryan@partners.org
SOURCE: Vaccine, (21 Jun 2002) 20/21-22 (2720-2726).
Refs: 33
ISSN: 0264-410X CODEN: VACCDE
PUBLISHER IDENT.: S 0264-410X(02)00208-6
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB In order to compare the ability of transcutaneous and oral immunization strategies to induce **mucosal** and systemic immune responses, we inoculated mice transcutaneously with cholera toxin (CT) or the non-toxic B subunit of cholera toxin (**CtxB**), or orally with Peru2(pETR1), an attenuated vaccine strain of Vibrio cholerae expressing **CtxB**. In addition, we also evaluated dual immunization regimens (oral inoculation with transcutaneous boosting, and transcutaneous immunization with oral boosting) in an attempt to optimize induction of both **mucosal** and systemic immune responses. We found that transcutaneous immunization with purified **CtxB** or CT induces much more prominent systemic IgG anti-**CtxB** responses than does oral inoculation with a vaccine vector strain of V. cholerae expressing **CtxB**. In comparison, anti-**CtxB** IgA in serum, stool and bile were comparable in mice either transcutaneously or orally immunized. Overall, the most prominent systemic and **mucosal** anti-**CtxB** responses occurred in mice that were orally primed with Peru2(pETR1) and transcutaneously boosted with CT. Our results suggest that combination oral and transcutaneous immunization strategies may most prominently induce both **mucosal** and systemic humoral responses.

L95 ANSWER 17 OF 43 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001151320 EMBASE
TITLE: Escherichia coli heat-labile enterotoxin B subunit is a more potent **mucosal** adjuvant than its closely related homologue, the B subunit of cholera toxin.
AUTHOR: Millar D.G.; Hirst T.R.; Snider D.P.
CORPORATE SOURCE: D.G. Millar, Department of Medical Biophysics, Ontario Cancer Institute, 610 University Ave., Toronto, Ont. M5G 2M9, Canada. dmillar@uhnres.utoronto.ca
SOURCE: Infection and Immunity, (2001) 69/5 (3476-3482).
Refs: 29
ISSN: 0019-9567 CODEN: INFIBR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Although cholera toxin (Ctx) and Escherichia coli heat-labile enterotoxin

(Etx) are known to be potent **mucosal** adjuvants, it remains controversial whether the adjuvanticity of the holotoxins extends to their nontoxic, receptor-binding B subunits. Here, we have systematically evaluated the comparative adjuvant properties of highly purified recombinant **EtxB** and **CtxB**. **EtxB** was found to be a more potent adjuvant than **CtxB**, stimulating responses to hen egg lysozyme when the two were coadministered to mice intranasally, as assessed by enhanced serum and secretory antibody titers as well as by stimulation of lymphocyte proliferation in spleen and draining lymph nodes. These results indicate that, although structurally very similar, **EtxB** and **CtxB** have strikingly different immunostimulatory properties and should not be considered equivalent as prospective vaccine adjuvants.

L95 ANSWER 18 OF 43 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001302228 EMBASE
TITLE: Local production of anti-Vibrio cholerae **mucosal** antibody in reproductive tract tissues after cholera.
AUTHOR: Ryan E.T.; Bridges E.A.; Crean T.I.; Gausia K.; Hamadani J.D.; Aziz A.; Hawkes S.; Begum M.; Bogaerts J.; Faruque S.M.; Salam M.A.; Fuchs G.J.; Calderwood S.B.
CORPORATE SOURCE: Dr. E.T. Ryan, Tropical and Geographic Med. Center, Division of Infectious Diseases, Massachusetts General Hospital, 55 Fruit St., Boston, MA 02114, United States. etryan@partners.org
SOURCE: Journal of Infectious Diseases, (1 Sep 2001) 184/5 (643-647).
Refs: 15
ISSN: 0022-1899 CODEN: JIDIAQ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
048 Gastroenterology
052 Toxicology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB To investigate whether intestinal presentation of an antigen by Vibrio cholerae, a noninvasive organism, could induce an anatomically distant **mucosal** immune response in reproductive tract tissues, the endocervical immune responses of women in Bangladesh were evaluated after cholera. Endocervical secretions were analyzed for secretory IgA (sIgA) antibody against the B subunit of cholera toxin (**CtxB**) in 9 women with cholera and 8 women with diarrhea caused by neither V. cholerae nor heat labile enterotoxin-producing Escherichia coli. Women infected with V. cholerae developed significant sIgA anti-**CtxB** responses in endocervical samples (P .ltoreq. .02). Antibody subtype analysis of endocervical IgA was consistent with local **mucosal** production (P .ltoreq. .001). Women with cholera did not develop sIgA anti-**CtxB** responses in serum. The ability to generate specific **mucosal** immune responses in reproductive tract tissues after intestinal presentation of antigen could facilitate development of vaccines effective against reproductive tract pathogens.

L95 ANSWER 19 OF 43 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 93030821 EMBASE
DOCUMENT NUMBER: 1993030821
TITLE: Reduction in oral immunogenicity of cholera toxin B subunit by N-terminal peptide addition.
AUTHOR: Dertzbaugh M.T.; Elson C.O.
CORPORATE SOURCE: U.S. Army Medical Research, Institute of Infectious

Diseases,Frederick, MD 21702-5011, United States
SOURCE: Infection and Immunity, (1993) 61/2 (384-390).
ISSN: 0019-9567 CODEN: INFIBR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The **mucosal** adjuvanticity of cholera toxin and the potential of the B subunit of cholera toxin (**CtxB**) to serve as an oral vaccine carrier have prompted interest in the coupling of immunogenic peptides to this protein. The purpose of this study was to determine how such fusions affect the function of **CtxB**. Oligonucleotides were genetically fused to the 5' terminus of the **ctxB** gene to encode additional amino acids of 8, 12, and 24 residues in length. None of these additions affected the ability of **CtxB** to oligomerize, as determined by nondenaturing sodium dodecyl sulfate- polyacrylamide gel electrophoresis. Circular dichroism revealed no difference in conformation between the modified B subunits, regardless of the length of the addition. However, when compared with native **CtxB**, additions to the N terminus induced a consistent change in the net conformation of the protein. By using a competitive enzyme immunoassay, the affinity of the modified B subunits for G(M1) ganglioside was shown to gradually decrease with increasing length of the N-terminal addition. A similar pattern was observed for the ability of the chimeras to inhibit proliferation of concanavalin A- stimulated spleen cells in vitro, which is a previously described functional property of **CtxB** that is dependent on its binding to cells. Lastly, the oral immunogenicity of these chimeras was found to be less than that of native **CtxB**. These results indicate that large fusions to the N terminus of **CtxB** can significantly affect its biological properties and could reduce its value as a mechanism for effective **mucosal** immunization.

L95 ANSWER 20 OF 43 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2003:212246 BIOSIS
DOCUMENT NUMBER: PREV200300212246
TITLE: The B subunit of Escherichia coli heat-labile enterotoxin enhances CD8+ cytotoxic-T-lymphocyte killing of Epstein-Barr virus-infected cell lines.
AUTHOR(S): Ong, Kong-Wee; Wilson, A. Douglas; Hirst, Timothy R.; Morgan, Andrew J. (1)
CORPORATE SOURCE: (1) Department of Pathology and Microbiology, School of Medical Sciences, University of Bristol, Bristol, BS8 1TD, UK: andy.morgan@bristol.ac.uk UK
SOURCE: Journal of Virology, (April 2003, 2003) Vol. 77, No. 7, pp. 4298-4305. print.
ISSN: 0022-538X.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Epstein-Barr virus (**EBV**) is associated with a number of important human cancers, including nasopharyngeal carcinoma, gastric carcinoma, and Hodgkin's lymphoma. These tumors express a viral nuclear antigen, **EBV** nuclear antigen 1 (EBNA1), which cannot be presented to T cells in a major histocompatibility complex class I context, and the viral latent membrane proteins (LMPs). Although the LMPs are expressed in these tumors, no effective immune response is made. We report here that exposure to the cholera-like enterotoxin B subunit (**EtxB**) in **EBV**-infected lymphoblastoid cell lines (LCLs) enhances their susceptibility to killing by LMP-specific CD8+ cytotoxic T

lymphocytes (CTLs) in a HLA class I-restricted manner. CTL killing of LCLs is dramatically increased through both transporter-associated protein-dependent and -independent epitopes after **EtxB** treatment. The use of mutant B subunits revealed that the enhanced susceptibility of LCLs to CTL killing is dependent on the B subunit's interaction with GM1 but not its signaling properties. These important findings could underpin the development of novel approaches to treating **EBV**-associated malignancies and may offer a general approach to increasing the presentation of other tumor and viral antigens.

L95 ANSWER 21 OF 43 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2002:223178 BIOSIS
DOCUMENT NUMBER: PREV200200223178
TITLE: Construction and **mucosal** immunogenicity of dimeric **pertussis** toxin-S1/S1 antigens genetically linked to cholera toxin A2/B.
AUTHOR(S): Salloum, D. F. (1); Lee, S. F. (1); Halperin, S. A. (1)
CORPORATE SOURCE: (1) Dalhousie University, Halifax, NS Canada
SOURCE: Abstracts of the General Meeting of the American Society for Microbiology, (2001) Vol. 101, pp. 335. http://www.asmusa.org/mtgsrc/generalmeeting.htm. print. Meeting Info.: 101st General Meeting of the American Society for Microbiology Orlando, FL, USA May 20-24, 2001 ISSN: 1060-2011.
DOCUMENT TYPE: Conference
LANGUAGE: English
AB Induction of a protective humoral immune response at **mucosal** surfaces, the initial barrier to most pathogens, is not readily achieved by systemic or **mucosal** administration of **vaccine** antigens. Increase in the incidence of whooping cough, a **vaccine** preventable disease caused by Bordetella pertussis has necessitated studies into the development of a new **vaccine**. In this work, the capacity of cholera toxin A2/B (CtxA2B) as a carrier for **mucosal** delivery of **vaccine** antigens was exploited to construct a chimeric fusion consisting of two in tandem copies of DNA encoding a 179 amino acid fragment of the N-terminus pertussis toxin S1 subunit. DNA encoding a non-toxic **GM1-binding** entity of cholera toxin CtxA/2B was cloned downstream of the S1/S1 fusion creating a S1/S1/CtxA2B genetic fusion. The S1/S1/CtxA2B fragment was subsequently cloned downstream to the maltose-binding protein (MBP) gene in pMALp. In-frame fusion was demonstrated by Western blotting and **GM1-binding** ELISA. Expression of MBP/S1/S1/CtxA2B was induced by IPTG and the chimeric protein was solubilized and isolated using 6M urea. SDS-PAGE and Western blotting confirmed isolation of the chimeric protein. **GM1-binding** ELISA demonstrated that the fusion protein is associating with the Ctx B-pentamer, forming the desired macromolecule. Intranasal administration of the MBP/S1/S1/CtxA2B chimera induced a **mucosal** (salivary sIgA) and a systemic (serum IgG) immune response to PT and CT in female BALB/c mice. In conclusion, a divalent pertussis toxin S1 fragment was successfully fused to cholera toxin A/2B and the chimeric protein, purified from Escherichia coli induces a **mucosal** and systemic immune response.

L95 ANSWER 22 OF 43 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:270440 BIOSIS
DOCUMENT NUMBER: PREV199900270440
TITLE: Intranuclear delivery of an antiviral peptide mediated by the B subunit of Escherichia coli heat-labile enterotoxin.
AUTHOR(S): Loregian, Arianna; Papini, Emanuele; Satin, Barbara; Marsden, Howard S.; Hirst, Timothy R.; Palu, Giorgio (1)
CORPORATE SOURCE: (1) Institute of Microbiology, University of Padua, 35121,

Padua Italy
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (April 27, 1999) Vol. 96, No. 9, pp. 5221-5226.
ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We report an intracellular peptide delivery system capable of targeting specific cellular compartments. In the model system we constructed a chimeric protein consisting of the nontoxic B subunit of Escherichia coli heat-labile enterotoxin (**EtxB**) fused to a 27-mer peptide derived from the DNA polymerase of **herpes** simplex virus 1. Viral DNA synthesis takes places in the nucleus and requires the interaction with an accessory factor, UL42, encoded by the virus. The peptide, designated Pol, is able to dissociate this interaction. The chimeric protein, **EtxB** -Pol, retained the functional properties of both **EtxB** and peptide components and was shown to inhibit viral DNA polymerase activity in vitro via disruption of the polymerase-UL42 complex. When added to virally infected cells, **EtxB**-Pol had no effect on adenovirus replication but specifically interfered with **herpes** simplex virus 1 replication. Further studies showed that the antiviral peptide localized in the nucleus, whereas the **EtxB** component remained associated with vesicular compartments. The results indicate that the chimeric protein entered through endosomal acidic compartments and that the Pol peptide was cleaved from the chimeric protein before being translocated into the nucleus. The system we describe is suitable for delivery of peptides that specifically disrupt protein-protein interactions and may be developed to target specific cellular compartments.

L95 ANSWER 23 OF 43 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:414747 BIOSIS
DOCUMENT NUMBER: PREV199900414747
TITLE: Mucosal immunogenicity and adjuvant activity of the recombinant A subunit of the Escherichia coli heat-labile enterotoxin.
AUTHOR(S): de Haan, L.; Holtrop, M.; Verweij, W. R.; Agsteribbe, E.; Wilschut, J. (1)
CORPORATE SOURCE: (1) Department of Physiological Chemistry, Groningen Utrecht Institute for Drug Exploration (GUIDE), University of Groningen, Antonius Deusinglaan 1, 9713 AV, Groningen Netherlands
SOURCE: Immunology, (Aug., 1999) Vol. 97, No. 4, pp. 706-713.
ISSN: 0019-2805.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The Escherichia coli heat-labile enterotoxin (LT) is an exceptionally effective mucosal immunogen and mucosal immunoadjuvant towards coadministered antigens. Although, in general, the molecular basis of these properties is poorly understood, both the toxic ADP-ribosylation activity of the LTA subunit and the cellular toxin receptor, ganglioside, **GM1-binding** properties of the LTB-pentamer have been suggested to be involved. In recent studies we found that **GM1-binding** is not essential for the adjuvanticity of LT, suggesting an important role for the LTA subunit in immune stimulation. We now describe the immunomodulatory properties of recombinant LTA molecules with or without ADP-ribosylation activity, LTA(His)10 and LTA-E112K (His)10, respectively. These molecules were expressed as fusion proteins with an N-terminal His-tag to allow simple purification on nickel-chelate columns.

Their immunogenic and immunoadjuvant properties were assessed upon intranasal administration to mice, and antigen-specific serum immunoglobulin-isotype and -subtype responses and mucosal secretory immunoglobulin A (IgA) responses were monitored using enzyme-linked immunosorbent assay. With respect to immunogenicity, both LTA(His)10 and LTA-E112K(His)10 failed to induce antibody responses. On the other hand, immunization with both LT and the non-toxic LT-E112K mutant not only induced brisk LTB-specific, but also LTA-specific serum and mucosal antibody responses. Therefore, we conclude that linkage of LTA to the LTB pentamer is essential for the induction of LTA-specific responses. With respect to adjuvanticity, both LTA(His)10 and LTA-E112K(His)10 were found to stimulate serum and mucosal antibody responses towards coadministered **influenza** subunit antigen. Remarkably, responses obtained with LTA(His)10 were comparable in both magnitude and serum immunoglobulin isotype and subtype distributions to those observed after coimmunization with LT, LT-E112K, or recombinant LTB. We conclude that LTA, by itself, can act as a potent adjuvant for intranasally administered antigens in a fashion independent of ADP-ribosylation activity and association with the LTB pentamer.

L95 ANSWER 24 OF 43 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:257406 BIOSIS
DOCUMENT NUMBER: PREV199800257406
TITLE: Mutational analysis of the role of ADP-ribosylation activity and **GM1-binding** activity in the adjuvant properties of the Escherichia coli heat-labile enterotoxin towards intranasally administered keyhole limpet hemocyanin.
AUTHOR(S): de Haan, Lolke; Feil, Ingeborg K.; Verweij, Willem R.; Holtrop, Marijke; Hol, Wim G. J.; Agsteribbe, Etienne; Wilschut, Jan (1)
CORPORATE SOURCE: (1) Dep. Physiological Chemistry, Groningen Utrecht Inst. Drug Exploration, Univ. Groningen, Antonius Deusinglaan 1, 9713 AV Groningen Netherlands
SOURCE: European Journal of Immunology, (April, 1998) Vol. 28, No. 4, pp. 1243-1250.
ISSN: 0014-2980.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The Escherichia coli heat-labile enterotoxin (LT) is known for its potent mucosal immunoadjuvant activity towards co-administered antigens. LT is composed of one A subunit, which has ADP-ribosylation activity, and a homopentameric B subunit, which has high affinity for the toxin receptor, ganglioside GM1. In previous studies, we have investigated the role of the LTA and LTB subunits in the adjuvanticity of LT towards **influenza** virus hemagglutinin (HA), administered intranasally to mice. We now studied the adjuvant properties of LT and LT variants towards keyhole limpet hemocyanin (KLH), which, in contrast to HA, does not bind specifically to mucosal surfaces. It is demonstrated that LT mutants without ADP-ribosylation activity, as well as LTB, retain mucosal immunoadjuvant activity when administered intranasally to mice in conjunction with KLH. As with **influenza** HA, adjuvanticity of LTB required **GM1-binding** activity, whereas **GM1-binding** was not essential for adjuvant activity of LT. Furthermore, we found that also recombinant LTA alone acts as a potent mucosal adjuvant, and that this adjuvanticity is independent of ADP-ribosylation activity. It is concluded that binding of the antigen to mucosal surfaces does not play an essential role in the immunostimulation by LT and LT variants, and that both recombinant LTA and LTB represent powerful nontoxic mucosal adjuvants.

L95 ANSWER 25 OF 43 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:392520 BIOSIS
DOCUMENT NUMBER: PREV199800392520
TITLE: Role of **GM1 binding** in the mucosal immunogenicity and adjuvant activity of the Escherichia coli heat-labile enterotoxin and its B subunit.
AUTHOR(S): De Haan, L.; Verweij, W. R.; Feil, I. K.; Holtrop, M.; Hol, W. G. J.; Agsteribbe, E.; Wischut, J. (1)
CORPORATE SOURCE: (1) Dep. Physiol. Chem., Groningen Utrecht Inst. Drug Exploration, Univ. Groningen, Antoinius Deusinglaan 1, 9713 AV Groningen Netherlands
SOURCE: Immunology, (July, 1998) Vol. 94, No. 3, pp. 424-430. ISSN: 0019-2805.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Escherichia coli (E. coli) heat-labile toxin (LT) is a potent mucosal immunogen and immunoadjuvant towards co-administered antigens. LT is composed of one copy of the A subunit, which has ADP-ribosylation activity, and a homopentamer of B subunits, which has affinity for the toxin receptor, the ganglioside GM1. Both the ADP-ribosylation activity of LTA and **GM1 binding** of LTB have been proposed to be involved in immune stimulation. We investigated the roles of these activities in the immunogenicity oil recombinant LT or LTB upon intranasal immunization of mice using LT/LTB mutants, lacking either ADP-ribosylation activity, **GM1-binding** affinity, or both. Likewise, the adjuvant properties of these LT/LTB variants towards **influenza** virus subunit antigen were investigated. With respect to the immunogenicity of LT and LTB, we found that **GM1-binding** activity is essential for effective induction of anti-LTB antibodies. On the other hand, an LT mutant lacking ADP-ribosylation activity retained the immunogenic properties of the native toxin, indicating that ADP ribosylation is not critically involved. Whereas adjuvanticity of LTB was found to be directly related to **GM1-binding** activity, adjuvanticity of LT was found to be independent of **GM1-binding** affinity. Moreover, a mutant lacking both **GM1-binding** and ADP-ribosylation activity, also retained adjuvanticity. These results demonstrate that neither ADP-ribosylation activity nor **GM1-binding** are essential for adjuvanticity of LT, and suggest an ADP-ribosylation-independent adjuvant effect of the A subunit.

L95 ANSWER 26 OF 43 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:276413 BIOSIS
DOCUMENT NUMBER: PREV199800276413
TITLE: **Affinity** purification of recombinant cholera toxin B subunit oligomer expressed in Bacillus brevis for potential human use as a **mucosal** adjuvant.
AUTHOR(S): Yasuda, Yoko (1); Matano, Keiko; Asai, Toru; Tochikubo, Kunio
CORPORATE SOURCE: (1) Dep. Microbiol., Nagoya City Univ. Med. Sch., Mizuho-ku, Nagoya 467-8601 Japan
SOURCE: FEMS Immunology and Medical Microbiology, (April, 1998) Vol. 20, No. 4, pp. 311-318. ISSN: 0928-8244.
DOCUMENT TYPE: Article
LANGUAGE: English
AB For use as a **mucosal** adjuvant for human **vaccines**, a simple method has been developed for the affinity purification of recombinant cholera toxin B subunit which had been expressed in a safe host, Bacillus brevis. Recombinant cholera toxin B subunit, adsorbed quantitatively to a D-galactose-agarose column. was eluted with an 0.1-0.4

M D-galactose gradient with a yield of > 90%. The cholera toxin B subunit preparation was similar to the native cholera toxin B subunit with respect to **GM1 binding** ability, remarkable stability of the pentamer, and the dissociation-reassociation property by shifting pHs. Crosslinking experiments with glutaraldehyde demonstrated that the pentameric form was predominant; tetrameric, trimeric, dimeric and monomeric forms were detected to a lesser extent, and additionally 10- and 15-mers were observed depending on the concentration of the cholera toxin B subunit.

L95 ANSWER 27 OF 43 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1997:25812 BIOSIS
DOCUMENT NUMBER: PREV199799325015
TITLE: Use of Vibrio spp. for expression of Escherichia coli enterotoxin B subunit fusion proteins: Purification and characterization of a chimera containing a C-terminal fragment of DNA polymerase from **herpes** simplex virus type 1.
AUTHOR(S): Loregian, Arianna; Hirst, Timothy R.; Marsden, Howard S.; Palu, Giorgio (1)
CORPORATE SOURCE: (1) Inst. Microbiol., Univ. Padova, via Gabelli 63, 35121 Padua Italy
SOURCE: Protein Expression and Purification, (1996) Vol. 8, No. 3, pp. 381-389.
ISSN: 1046-5928.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The nontoxic B subunit of Escherichia coli heat-labile enterotoxin (**EtxB**) is a convenient carrier molecule for the attachment and delivery of heterologous peptides into eukaryotic cells. To evaluate the properties of such **EtxB**-based fusion proteins an efficient method for their production and purification is required. High-level production and purification of native **EtxB** has been achieved using heterologous expression and secretion in a marine Vibrio (Amin, T., and Hirst, T. R., 1994, Protein Expression Purif. 5, 198 204). However, the use of this method to isolate **EtxB** fusion proteins has been precluded because of their susceptibility to degradation by extracellular proteases secreted by members of the Vibrionaceae. In this paper a method is described for production of EtxBpol, comprising the enterotoxin B subunit linked to a 27-residue C-terminal fragment of Pol, the catalytic subunit of DNA polymerase of **herpes** simplex virus type 1 (**HSV**-1). Following assessment of the relative efficacy of different Vibrio strains as hosts for EtxBpol expression, the chimera was produced at the highest level of 3.5 mg/liter by cultures of Vibrio sp.60. Addition of 0.3 mm EDTA to the growth medium blocked proteolysis of the secreted **EtxB**-pol fusion protein, which was then purified to homogeneity using ammonium sulfate fractionation and hydrophobic interaction chromatography, with a yield of 57%. Purified **EtxB**-pol reacted with both anti-**EtxB** and anti-Pol peptide antibodies, and was able to specifically bind UL42, a processivity factor which normally binds to the C-terminal region of **HSV**-1 Pol. This modified method for expression and purification of **EtxB**-pol should be of general utility for the preparation of other **EtxB**-based fusion proteins.

L95 ANSWER 28 OF 43 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1995:131767 BIOSIS
DOCUMENT NUMBER: PREV199598146067
TITLE: Specificity of the protein secretory apparatus: Secretion of the heat-labile enterotoxin B subunit pentamers by different species of gram- bacteria.
AUTHOR(S): Michel, Linda Overbye; Sandkvist, Maria; Bagdasarian,

Michael (1)
CORPORATE SOURCE: (1) S110 Plant Biol. Build., Michigan State Univ., East Lansing, MI 48824 USA
SOURCE: Gene (Amsterdam), (1995) Vol. 152, No. 1, pp. 41-45. ISSN: 0378-1119.
DOCUMENT TYPE: Article
LANGUAGE: English
AB The B-subunit pentamer(s) (EtxBp) of Escherichia coli heat-labile enterotoxin (LT) are secreted from Vibrio cholerae via the general secretion pathway (GSP), but remain periplasmic in E. coli. In order to determine if other Gram-bacteria were also able to secrete the ExtBp, the **etxB** gene, which encodes **EtxB** was introduced into different bacteria. Of the bacteria examined, most species of Vibrio and Aeromonas were able to secrete this protein through the outer membrane; other Gram- genera, including Erwinia, Klebsiella and Xanthomonas were not, even though they encode GSP genes homologous to those of V. cholerae. Thus, the ability to recognize the EtxBp as a secretable protein is confined to bacteria that were identified as being closely related to V. cholerae by examination of their 5S rRNA (MacDonell and Colwell, Syst. Appl. Microbiol. 6 (1985) 171-182).

L95 ANSWER 29 OF 43 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:479508 BIOSIS
DOCUMENT NUMBER: PREV199497492508
TITLE: Specific inhibition of **herpes** virus replication by receptor-mediated entry of an antiviral peptide linked to Escherichia coli enterotoxin B subunit.
AUTHOR(S): Marcello, Alessandro; Loregian, Arianna; Cross, Anne; Marsden, Howard; Hirst, Timothy R.; Palu, Giorgio (1)
CORPORATE SOURCE: (1) Inst. Microbiol., Univ. Padova, 35121 Padova Italy
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1994) Vol. 91, No. 19, pp. 8994-8998. ISSN: 0027-8424.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Mimetic peptides capable of selectively disrupting protein-protein interactions represent potential therapeutic agents for inhibition of viral and cellular enzymes. This approach was first suggested by the observation that the peptide YAGAVVNDL, corresponding to the carboxyl-terminal 9 amino acids of the small subunit of ribonucleotide reductase of **herpes** simplex virus, specifically inhibited the viral enzyme in vitro. Evaluation and use of this peptide as a potential antiviral agent has, however, been thwarted by its failure to inhibit virus replication in vivo, presumably because the peptide is too large to enter eukaryotic cells unaided. Here, we show that the nontoxic B subunit of Escherichia coli heat-labile enterotoxin can be used as a recombinant carrier for the receptor-mediated delivery of YAGAVVNDL into virally infected cells. The resultant fusion protein specifically inhibited **herpes** simplex virus type 1 replication and ribonucleotide reductase activity in quiescent Vero cells. Preincubation of the fusion protein with soluble GM1 ganglioside abolished this antiviral effect, indicating that receptor-mediated binding to the target cell is necessary for its activity. This provides direct evidence of the usefulness of carrier-mediated delivery to evaluate the intracellular efficacy of a putative antiviral peptide.

L95 ANSWER 30 OF 43 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:191598 BIOSIS
DOCUMENT NUMBER: PREV199497204598
TITLE: Cholera toxin B subunit-coated microparticles bind

selectively to **Peyer**'s patch M cells.
AUTHOR(S): Frey, Andreas (1); Reggio, Hubert; Weltzin, Richard A.; Lencer, Wayne I.; Neutra, Marian R.
CORPORATE SOURCE: (1) Dep. Pediatrics, Harvard Med. Sch., Boston, MA 02115 USA
SOURCE: Journal of Cellular Biochemistry Supplement, (1994) Vol. 0, No. 18 PART A, pp. 60.
Meeting Info.: Keystone Symposium on Molecular Events in Microbial Pathogenesis Santa Fe, New Mexico, USA January 8-14, 1994
ISSN: 0733-1959.
DOCUMENT TYPE: Conference
LANGUAGE: English

L95 ANSWER 31 OF 43 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:216497 BIOSIS
DOCUMENT NUMBER: PREV199497229497
TITLE: Efficient extracellular production of hybrid E. coli heat-labile enterotoxin B subunits in a marine vibrio.
AUTHOR(S): Marcello, Alessandro (1); Loregian, Arianna; Palu, Giorgio; Hirst, Timothy R.
CORPORATE SOURCE: (1) Inst. Microbiol., Univ. Padua, via Gabelli 63, 35121 Padua Italy
SOURCE: FEMS Microbiology Letters, (1994) Vol. 117, No. 1, pp. 47-51.
ISSN: 0378-1097.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Escherchia coli heat-labile enterotoxin B subunit (**EtxB**) has been proposed as a potential protein carrier for the delivery of heterologous peptides to target cells, particularly for the oral delivery of epitopes to the mucosal immune system. In this study, two extensions to the C-terminus of **EtxB** were genetically engineered that correspond to a well-characterized neutralising epitope of glycoprotein D from **herpes** simplex virus (**EtxB**-gD) and to the C-terminal nine amino acids from the 38 kDa subunit of **HSV** -encoded ribonucleotide reductase (**EtxB**-R2). Here we describe the extracellular secretion of the two hybrid **EtxBs** from a marine Vibrio harbouring a broad-host range inducible expression vector containing the hybrid genes. Large amounts of intact fusion proteins (15-20 mg per liter of culture) were secreted into the medium upon induction. These hybrid proteins maintained the receptor-binding activity of the native toxin as well as being cross-reactive with anti-**EtxB** and anti-heterologous peptide monoclonal antibodies.

L95 ANSWER 32 OF 43 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1992:380992 BIOSIS
DOCUMENT NUMBER: BR43:47942
TITLE: CLONING AND CHARACTERIZATION OF A HAEMOPHILUS-**INFLUENZAE** TYPE B ADHESIN.
AUTHOR(S): WEINSTEIN D L; TURKOVSKI S M; KERRY C F; KRIVAN H C; SAMUEL J E
CORPORATE SOURCE: MICROCARB INC., GAITHERSBURG, MD.
SOURCE: 92ND GENERAL MEETING OF THE AMERICAN SOCIETY FOR MICROBIOLOGY, NEW ORLEANS, LOUISIANA, USA, MAY 26-30, 1992.
ABSTR GEN MEET AM SOC MICROBIOL, (1992) 92 (0), 136.
CODEN: AGMME8.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L95 ANSWER 33 OF 43 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2003-221541 [21] WPIDS
DOC. NO. CPI: C2003-056312
TITLE: New compositions comprising nucleic acid adjuvants, useful in immunization techniques, particularly for eliciting or enhancing an immune response against an antigen in a human.
DERWENT CLASS: B04 D16
INVENTOR(S): ARRINGTON, J E; HAYNES, J R
PATENT ASSIGNEE(S): (POWD-N) POWDERJECT VACCINES INC
COUNTRY COUNT: 98
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003004055	A2	20030116	(200321)*	EN	143

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003004055	A2	WO 2001-US43151	20011126

PRIORITY APPLN. INFO: US 2000-724315 20001127
AB WO2003004055 A UPAB: 20030328
NOVELTY - A composition comprising:
(a) a first nucleic acid sequence that is a truncated A subunit coding region obtained or derived from a bacterial ADP-ribosylating exotoxin; and
(b) a second nucleic acid sequence that is a truncated B subunit coding region obtained or derived from a bacterial ADP-ribosylating exotoxin, is new.
DETAILED DESCRIPTION - A new composition comprises:
(a) a first nucleic acid sequence that is a truncated A subunit coding region obtained or derived from a bacterial ADP-ribosylating exotoxin; and
(b) a second nucleic acid sequence that is a truncated B subunit coding region obtained or derived from a bacterial ADP-ribosylating exotoxin.
Each of the truncated subunit coding regions has a 5' deletion, and encodes a subunit peptide not having an amino terminal bacterial signal peptide.
INDEPENDENT CLAIMS are also included for the following:
(1) a particle delivery device loaded with the novel **vaccine** composition; and
(2) enhancing an immune response against an antigen in a subject.
ACTIVITY - Adjuvant.
A DNA **vaccine** vector encoding the M2 protein of **influenza** A was employed to test the adjuvant effects of the CT-encoding adjuvant vectors, particularly the pPJV2002, pPJV2003 and pPJV2006 adjuvant vectors. Groups of mice were administered with pM2-FL DNA vector alone, or with the pM2-FL DNA vector and one or more of the adjuvant vectors. Results showed that all experimental groups immunized with a formulation containing one or more of the CT-encoding adjuvant

vectors exhibited an increased geometric mean titer following the booster immunization relative to control animals immunized with the M2 vector alone.

MECHANISM OF ACTION - **Vaccine.**

USE - The composition is useful for eliciting an immune response against an antigen, or for manufacturing a medicament for enhancing an immune response in a vertebrate subject (specifically a human) against an antigen (claimed). The composition is particularly useful as nucleic acid adjuvants for use in immunization techniques.

Dwg.0/14

L95 ANSWER 34 OF 43 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2003-129162 [12] WPIDS
DOC. NO. CPI: C2003-032959
TITLE: Aerosolizer used for treating e.g. otitis media, comprises **immunogenic** intranasal composition and a **mucosal** adjuvant or delivery system.
DERWENT CLASS: A96 B04
INVENTOR(S): GU, X
PATENT ASSIGNEE(S): (USSH) US DEPT HEALTH & HUMAN SERVICES
COUNTRY COUNT: 4
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002089839	A1	20021114	(200312)*	EN	61

W: AU CA JP US

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002089839	A1	WO 2001-US32331	20011016

PRIORITY APPLN. INFO: US 2001-288695P 20010503
AB WO 200289839 A UPAB: 20030218

NOVELTY - Aerosolizer comprises an **immunogenic** composition which comprises nontypeable Haemophilus **influenza** or Moraxella catarrhalis lipooligosaccharide (LOS) and **mucosal** adjuvant or delivery system. At least one primary O-linked fatty acid from LOS is removed to form detoxified LOS (dLOS) and an **immunogenic** carrier covalently linked to it by a linker.

ACTIVITY - Antiinflammatory; Auditory; Antibacterial.

MECHANISM OF ACTION - **Vaccine.**

Lipooligosaccharide (LOS) of (nontypeable Haemophilus **influenza**) (NTHi) strain 9274 was extracted from cells by hot phenol water and then purified by gel filtration as described in Gu, X.X et. al. 1995 Infect Immun 63:4115-4120. Detoxification of LOS, conjugation of dLOS to TT and characterization of dLOS-TT from strain 9274 were effected as described in Gu, X.X et. al. 1995 Infect Immun 64:4047-4053. The composition of dLOS-TT comprised dLOS (638 mu g) and TT (901 mu g) in a molar ratio of 35:1. For the enumeration of LOS-specific **immunoglobulin**-producing cells, the numbers of LOS-specific IgA-producing cells in nasal associated lymphoid tissue, normal prostate, submandibular glands, spleen, cervical lymph nodes, lung, and small intestine were determined with ELISPOT assay as described in Kodama, S. et. al. 2000 Infect Immun 68:2294-2300.

To examine the effect of the dLOS-TT **vaccine** on NTHi clearance in nasopharynx, the mice immunized with different antigens were challenged with the homologous strain 9274. The strain was grown on

chocolate agar at 37 deg. C under 5% CO2 for 16 hours and then 3 - 5 clones were transferred to another plate and incubated for 4 hours. A bacterial suspension was prepared to the concentration of 4-6 multiply 106 CFU/ml and the mice were intranasally inoculated with the bacterial suspension (10 mu l). To investigate correlation between antibody levels and bacterial clearance of strain 9274, saliva was collected. To examine the cross-reactivity of antibodies in saliva elicited by the **vaccine** against heterologous NTHi strains, the homologous NTHi strains 9274 were suspended in PBS to an optical density of 65% transmission. Cholera toxin (CT) acted as control. Results of GM antibody ELISA titers for dLOS-TT+CT/dLOS-CT/CT were 63/6/5.

USE - Used for treating otitis media, other **respiratory** disease caused by NTHi or M. catarrhalis infection and sinusitis in children and in conjugate **vaccine** and inhibits colonization by NTHi or Moraxella catarrhalis.

ADVANTAGE - The aerosolizer induces an **immunological** response.

Dwg.0/14

L95 ANSWER 35 OF 43 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-657564 [70] WPIDS
DOC. NO. CPI: C2002-184545
TITLE: Novel **immunogen** for transcutaneous immunization useful for treating traveler's diarrhea, comprises antigens in effective amounts to induce immune response against strains of enterotoxigenic Escherichia coli.
DERWENT CLASS: B04 D16
INVENTOR(S): CASSELS, F J; GLENN, G M
PATENT ASSIGNEE(S): (USSA) US SEC OF ARMY
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002064162	A2	20020822	(200270)*	EN	132

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002064162	A2	WO 2002-US4254	20020213

PRIORITY APPLN. INFO: US 2001-310483P 20010808; US 2001-268016P 20010213; US 2001-304110P 20010711; US 2001-310447P 20010808

AB WO 200264162 A UPAB: 20021031

NOVELTY - An **immunogen** (I) for transcutaneous immunization, comprising one or more antigens in effective amounts to induce an immune response against one or more strains of enterotoxigenic Escherichia coli (ETEC), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a **vaccine** (II) suitable for transcutaneous immunization ((II) is comprised of a patch and (I));

(2) a subunit **vaccine** (III) suitable for transcutaneous immunization ((III) is comprised of (I) which is chemically synthesized, recombinantly produced, at least partially purified, or its combinations in cell-free form);

(3) a whole-cell **vaccine** (IV) suitable for transcutaneous immunization ((IV) is comprised of (I) in whole-cell form); and

(4) use of effective amounts of one or more antigens (V) and at least one adjuvant (VI), for manufacture of an **immunogen** or **vaccine** which induces immune response against one or more strains of ETEC by transcutaneous immunization.

ACTIVITY - Antidiarrheic; Antibacterial; Protozoacide; Virucide; Hepatotropic; Antiinflammatory.

MECHANISM OF ACTION - **Vaccine**; Inducer of immune response (claimed).

Mucosal immune response to E. coli colonization factor antigen, CS3 after transcutaneous immunization (TCI) was tested. The **mucosal** (gastrointestinal) immune response elicited by TCI with ETEC subunit **vaccines** was characterized. A study was conducted to determine if TCI with CS3 with and without LTR192G adjuvant resulted in the production of antibodies in gastric **mucosa**. Mice were shaved (48 hours in advance) at the base of the tail, and the skin was hydrated and tape was stripped 10 times. **Vaccine**-loaded patches were placed over the pretreated skin. Groups of mice received patches with the following formulations: phosphate buffered saline (PBS); 25 micro g CS3 alone; and 25 micro g CS3/10 micro g LTR192G. The patches were applied overnight.

A separate group of mice was **vaccinated** by intradermal injection of 25 micro g CS3. All mice received three **vaccinations** on day 0, 14 and 28. Fresh fecal samples were collected 7 days after the third immunization (day 35). The results showed that **vaccination** with CS3 alone did not elicit antigen-specific antibody, with the exception of one animal. Mice **vaccinated** with CS3/LTR192G developed detectable fecal **immunoglobulin** (Ig)G to CS3.

USE - (I), (II), (III) or (IV) Is useful for inducing an immune response against one or more strains of ETEC, and to treat and/or prevent one or more disease symptoms associated with traveler's diarrhea, where the methods further comprise chemical and/or physical penetration enhancement. (V) or (VI) is useful for manufacture of an **immunogen** or **vaccine** which induces an immune response against one or more strains of ETEC (claimed).

(II) Is useful for treating against infections by pathogens such as, for example ETEC. (I), (II), (III) or (IV) is also useful for treating travelers' diseases such as campylobacteriosis (Campylobacter jejuni), giardiasis (Giardia intestinalis), **hepatitis** (**hepatitis** virus A or B), malaria (Plasmodium falciparum, P. ovale, and P. malariae), shigellosis (Shigella boydii, S. dysenteriae, S. flexneri, and S. sonnei), and viral gastroenteritis (rotavirus).

Dwg.0/27

L95 ANSWER 36 OF 43 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-372091 [40] WPIDS
DOC. NO. CPI: C2002-105336
TITLE: An **immunogenic** complex for use as **immunostimulating** complexes (iscoms) or matrixes comprises a glycoside and a lipid integrated into the complex.
DERWENT CLASS: B04 C06 D16
INVENTOR(S): DALSGAARD, K; KAASTRUP, P; LOEWENADLER, B; LYCKE, N; MC MOWAT, A
PATENT ASSIGNEE(S): (ISCO-N) ISCONOVA AB
COUNTRY COUNT: 97

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002026255	A1	20020404	(200240)*	EN	64

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001092493 A 20020408 (200252)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002026255	A1	WO 2001-SE2117	20011001
AU 2001092493	A	AU 2001-92493	20011001

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001092493	A	Based on	WO 200226255

PRIORITY APPLN. INFO: SE 2000-3538 20000929

AB WO 200226255 A UPAB: 20020626

NOVELTY - An **immunogenic** complex comprising one glycoside and one lipid, integrated into an iscom complex or matrix and one antigen which is integrated into the iscom complex or coupled on to or mixed with the iscom complex or iscom matrix complex, also comprising an enzyme, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for an **immunogenic** composition comprising one or more excipient that are acceptable in pharmaceutical or veterinary products, where the complexes or components to be mixed may be placed in separate compartments.

ACTIVITY - None given.

MECHANISM OF ACTION - **Vaccine**.

For oral immunization, mice were fed on days 1,2,3,8,9 and 10 with iscoms or purified fusion proteins containing 4 micro g of CTA1-OVAp-DD, equivalent to 150ng of OVA 323-339. One group of mice received 750ng of OVA 323-339 on each occasion. In vivo and in vitro measurements are performed. Results showed that a targeted CT derivative can be incorporated into iscoms. the resulting combined vector is a potent adjuvant for inducing a wide range of immune responses to small amounts of peptide **immunogen** after **mucosal** and parenteral administration.

USE - The **immunogenic** complex is used for providing iscom complexes on to which antigens, enzymes and/or peptides or proteins which specifically bind to a receptor expressed on a cell capable of antigen presentation. The complex may also be used as an **immunogenic** matrix complex comprising one glycoside, a lipid onto which antigens, enzymes and/or peptides or proteins, which specifically bind to a receptor expressed on a cell capable of antigen presentation have been coupled.

ADVANTAGE - Combining iscoms and an enzyme, especially CTA1 and its derivatives, enhances adjuvant effects and the overall effect may be synergistic. The formulation is non-toxic and is highly **immunogenic** by a variety of **mucosal** and systemic routes.

Mice were immunized intranasally on three occasions 10 days apart, with iscoms or purified fusion proteins containing 4 micro g of

CTA1-OVAp-DD or CTA1R7K-OVAp-DD (equivalent to 150 ng of OVA323-339 in total volume of 20 micro l. Control groups of mice received the equivalent of 150ng of OVA peptide. Results showed a synergistic effect in that the effect in the level of proliferation and production of IFN-gamma when CTA1-OVAp-DD iscoms are used is higher than the sum of the corresponding levels when CTA1R7K-OVA-pDD iscoms are used.
Dwg.0/8

L95 ANSWER 37 OF 43 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2002-641556 [69] WPIDS
DOC. NO. CPI: C2002-181137
TITLE: Orally administrable pharmaceutical compositions for producing immune responses hosts to antigens specific for pathogens, comprises an admixture of antigen, and non-toxic Escherichia coli heat labile enterotoxin as adjuvant.
DERWENT CLASS: B04 D16
INVENTOR(S): CLEMENTS, J D
PATENT ASSIGNEE(S): (USNA) US SEC OF NAVY
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6413523	B1	20020702	(200269)*		29

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 6413523	B1	CIP of	US 1989-360662	19890602
		Cont of	US 1993-906	19930106
			US 1995-394522	19950223

PRIORITY APPLN. INFO: US 1993-906 19930106; US 1989-360662 19890602; US 1995-394522 19950223

AB US 6413523 B UPAB: 20021026
NOVELTY - An orally administrable pharmaceutical composition (I) useful in producing a protective immune response in a host to an antigen specific for a pathogen, comprises an admixture of the antigen, and an adjuvant effective, non-toxic amount of Escherichia coli heat labile **enterotoxin** (**LT**), is new.

ACTIVITY - Antibacterial; Virucide; Fungicide; Protozoacide; Antihelmintic.

MECHANISM OF ACTION - **Vaccine**; Inducer of immune responses.

To test the potential of LT as an orally administered adjuvant with a biologically relevant antigen (u-v inactivated **Herpes** simplex virus type I (**HSVuv**)), four groups of mice were immunized as follows:

On day 0, group A received 0.5 ml of phosphate buffered saline (PBS) containing 5 mg of ovalbumin (OVA), 20 micro g of **HSV**(uv), and 25 micro g of LT; group B received 0.5 ml of PBS containing 20 Ag of **HSV**(uv) and 25 Mg of LT; group C received 0.5 ml of PBS containing 20 micro g of viable **HSV**; and group D received 0.5 ml of PBS containing 20 pg of **HSV**(uv).

This regimen was repeated on days 7 and 14. On day 21, animals were boosted intraperitoneally (i.p.) with 0.5 ml of PBS containing 1 micro g of **HSV**(uv) in 20% Maalox.

Serum IgG and **mucosal** IgA response were determined one week later for **HSV** by enzyme linked **immunosorbant** assay

(ELISA). Simultaneous administration of LT with **HSV**(uv) enhanced the serum IgG response against **HSV** (group A: 61.47 ng/ml, and group B: 81.74 ng/ml) when compared to animals immunized with **HSV** (uv) alone (group D: 54.46 ng/ml), or infected with viable **HSV** (group C: 27 ng/ml).

A **mucosal** anti-**HSV** IgA response was detected in animals receiving LT with the oral immunization in the presence of 5 mg of OVA, and in animals infected with viable **HSV**. There was no detectable anti-**HSV** IgA response in animals immunized with **HSV**(uv) without the OVA included. A virus neutralization assay was performed, in which African Green Monkey Kidney (AGMK) cells were seeded in 96-well tissue culture dishes at 5 multiply 104 cells/well. Sera of mice from the various groups were added to the cultures in two-fold serial dilutions.

Cells were then challenged with **HSV**-1 at a multiplicity of infection of 10 pfu/cell or mock infected in the presence of the mouse serum. After 18 hr, the ability of the mouse sera to neutralize **HSV**-1 infectivity was quantitated by counting the number of cells in each well which were rounded or spindle-shaped, the typical cytopathic effect (CPE) induced by **HSV**-1. The serum antibodies raised in mice immunized with LT and **HSV**(uv) with or without OVA, were able to protect AGMK cells against the cytopathic effects of **HSV** -1.

USE - (I) Is useful for increasing an immune response of a host to a specific pathogen or producing a protective immune response (**mucosal** immune response) to an antigen specific for a pathogen. The antigen is killed bacteria (Campylobacter sp.), virus (**herpes** or **influenza** virus), protozoa or fungi.

The admixture contains a buffer, and is administered as a single dose (claimed).

(I) Is useful for ablating the physiological or disease state caused by bacteria (e.g. Escherichia coli and Streptococcus pyogenes), fungi (e.g. Candida albicans and Aspergillus fumigatus), protozoa (Entamoeba histolytica and Trichomonas tenas), and helminths (such as Enterobius vermicularis, Trichuris trichiura, Ascaris lumbricoides and hookworms).

(I) Is useful for immune clearance of allergenic substances from **mucosal** surfaces.

ADVANTAGE - (I) Induces rapid and long-lasting immunity, compared to standard killed **vaccines** which exhibit a window of protection as short as six weeks, and measles **vaccine**. In (I), LT is an effective adjuvant having low toxicity, compared to cholera toxin.
Dwg.0/15

L95 ANSWER 38 OF 43 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-266110 [27] WPIDS
DOC. NO. CPI: C2001-080588
TITLE: Reproducible production of antigen-**mucosal** binding component (e.g. insulin-cholera toxin B) conjugates used e.g. to induce specific **immunological** tolerance, gives higher yields and is more economical.
DERWENT CLASS: B04 D16
INVENTOR(S): BOGSNES, A; DE JONGH, K; FORSTROM, J; PETERSEN, J S; PETRIE, C R
PATENT ASSIGNEE(S): (NOVO) NOVO NORDISK AS
COUNTRY COUNT: 93
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001022995	A1	20010405	(200127)*	EN	52

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000074048 A 20010430 (200142)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001022995	A1	WO 2000-DK531	20000928
AU 2000074048	A	AU 2000-74048	20000928

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000074048	A	Based on	WO 200122995

PRIORITY APPLN. INFO: DK 1999-1392 19990930

AB WO 200122995 A UPAB: 20010518
NOVELTY - Preparing products of conjugates between an antigen and **mucosal** binding components.

DETAILED DESCRIPTION - Products of conjugates between an antigen and **mucosal** binding components are prepared by:

(a) reacting the antigen with first crosslinkers to produce a mixture of crosslinker derivatives of the antigen;

(b) isolating the antigen derivatized with a single crosslinker residue;

(c) activating the isolated crosslinker derivative of the antigen;

(d) reacting the **mucosal** binding component with a second crosslinker to produce a mixture of crosslinker derivatives of the **mucosal** binding component; and

(e) reacting the activated crosslinker derivative of the antigen with the mixture of crosslinker derivatives of the **mucosal** binding component to produce the conjugates between the antigen and the **mucosal** binding component.

INDEPENDENT CLAIMS are also included for:

(1) products of conjugates between an antigen and a **mucosal** binding component in which the individual conjugate consists of one **mucosal** binding component conjugated to one or more antigens;

(2) products of conjugates between an insulin peptide and the cholera toxin B (CTB) subunit in which the individual conjugate consists of one CTB subunit conjugated to one or more insulin peptides; and

(3) the use of insulin-specific T-cell hybridoma assays to characterize antigen presenting potentiation of a conjugate between an antigen and a **mucosal** binding component.

ACTIVITY - **Immunosuppressive**. No biodata is provided.

MECHANISM OF ACTION - None given.

USE - The processes are used to prepare conjugates between antigen and **mucosal** binding components, e.g. insulin and CTB subunits, which are used in pharmaceutical compositions used to induce specific **immunological** tolerance in mammals (claimed) such as to suppress autoimmunity and as research tools to increase the understanding of specific **immunological** tolerance.

ADVANTAGE - The process produces conjugates that are more effective at inducing **immunological** tolerance at lower doses compared to the current methods, the processes are also more reproducible, give higher yields and are more economical.

Dwg.0/9

L95 ANSWER 39 OF 43 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2000-647400 [62] WPIDS
DOC. NO. CPI: C2000-195900
TITLE: Killing lymphoma cells using a **Gb3-binding** agent, especially verotoxin, useful for treating lymphomas such as a post-transplant lymphoproliferative disorder, at non-toxic doses.
DERWENT CLASS: B04 D16
INVENTOR(S): ARBUS, G; LINGWOOD, C A
PATENT ASSIGNEE(S): (HSCR-N) HSC RES & DEV LP
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000061183	A2	20001019	(200062)*	EN	63
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP NZ					
AU 2000037985	A	20001114	(200108)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000061183	A2	WO 2000-CA371	20000407
AU 2000037985	A	AU 2000-37985	20000407

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000037985	A Based on	WO 200061183

PRIORITY APPLN. INFO: US 1999-128670P 19990409
AB WO 200061183 A UPAB: 20001130
NOVELTY - A method of inducing lymphoma cell death (specifically in lymphoma cells of B cell origin such as **EBV** (Epstein-barr virus) positive cells) and treating a disorder characterized by infiltrating lymphoma cells comprising administration of an agent (I) which binds Gb3, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a kit comprising (I).

ACTIVITY - Cytostatic; anti-human **immunodeficiency** virus (HIV); nephrotropic; cardioactive; pulmonary.

The antiproliferative effects of verotoxins on human astrocytoma cells was studied. Results showed that cells most sensitive to VT1 in terms of growth inhibition were SF-539 and the least sensitive were SF-188. When treated with other members of the verotoxin family, including VT2 and VT2c, SF539 growth was inhibited. VT1 was the most potent species. Human cerebral endothelial cells were largely resistant to the growth inhibitory and cytotoxic effects of VT1. Only when doses as high as 100 ng/ml were used were endothelial cells inhibited. XF498 cells were considerably less sensitive to the B subunit than the VT1 holotoxin. By comparison, SF539 astrocytoma cells were significantly more sensitive to the B subunit alone than were XF498 astrocytoma cells, since 50% cell death was observed in the presence of 50 ng/ml.

MECHANISM OF ACTION - Induction of cell death and apoptosis and inhibition of protein synthesis in lymphoma cells.

USE - The method is specifically used for treating disorders

characterized by infiltrating lymphoma cells (specifically a lymphoma, especially a cutaneous T-cell disorder), by administration of (I) to the patient. The lymphoma to be treated is particularly Mycosis Fungoides, sezary syndrome, related cutaneous disease lymphomatoid papilosis or post-transplant lymphoproliferative disorder (PTLD), especially PTLD associated with renal, heart, lung or liver transplantation (all claimed). The method may also be used for treating lymphomas in HIV (human **immunodeficiency** virus) patients.

ADVANTAGE - (I) (especially verotoxins) have a potent anti-lymphoma effect in vitro and in vivo, and in particular are effective in the treatment of humans at non-toxic dosages. Typically Mycosis Fungoides lesions in humans were cleared without any observed adverse systemic effects by interdermal injection of verotoxin 1 (5 ng in 2 ml solution). Dwg.0/18

L95 ANSWER 40 OF 43 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1998-311399 [27] WPIDS
CROSS REFERENCE: 1992-315939 [38]; 1994-359522 [45]; 1995-394157 [51]; 1996-030801 [04]; 1996-049021 [05]; 1997-042808 [04]; 1998-217031 [19]; 1998-505588 [43]; 1999-105118 [09]; 1999-166635 [14]; 1999-579913 [49]
DOC. NO. CPI: C1998-095969
TITLE: Truncated **pneumococcal** surface protein and cholera toxin B sub-unit fusion protein - useful as an **immunogen** against Streptococcus **pneumoniae**.
DERWENT CLASS: B04 D16
INVENTOR(S): BRILES, D E; YOTHER, J L
PATENT ASSIGNEE(S): (UABR-N) UAB RES FOUND
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 5753463	A	19980519	(199827)*		22

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 5753463	A	CIP of	US 1991-656773	19910215
		Div ex	US 1992-835698	19920212
		Cont of	US 1993-72065	19930603
			US 1995-469434	19950606

PRIORITY APPLN. INFO: US 1992-835698 19920212; US 1991-656773 19910215; US 1993-72065 19930603; US 1995-469434 19950606
AB US 5753463 A UPAB: 20000405
A recombinant DNA molecule encoding a fusion protein comprising a truncated form of **pneumococcal** surface protein (PspA) and cholera toxin B subunit (CTB) is new, where the DNA molecule comprises a nucleotide sequence encoding the truncated PspA linked by an in-frame genetic fusion to a **ctxB** gene, and where the truncated PspA contains **immunoprotective** epitopes and up to 90% of the whole PspA protein, except for the cell membrane anchor region, the whole PspA protein having a defined sequence of 648 amino acids as given in the specification.

Also claimed are:
(a) a mutated strain of Streptococcus **pneumoniae** containing

the recombinant DNA molecule;
(b) plasmid pJY4163; and
(c) a method for producing the fusion protein, comprising transforming a bacterium selected from (a strain of) Streptococcus **pneumoniae** or (a strain of) E. coli with the recombinant DNA molecule and growing the transformed bacterium to express the fusion protein.
USE - The fusion protein is useful for providing an **immunogen** to protect neonates and children against S.**pneumoniae**. Most antigenic proteins of this strain are not **immunogenic** enough to provide protection. The antigenic epitopes of the fusion protein are directed against capsular polysaccharide antigens of S.**pneumoniae** , specifically it contains the protective epitopes of PspA. The protein can also be used in solid-phase **immunoadsorbent** assays, since it is readily bound to supports coated with monosialoganglioside GM1.
ADVANTAGE - The fusion protein is more **immunogenic** against S.**pneumoniae** than using PspA alone as the **immunogen**.
Dwg.0/7

L95 ANSWER 41 OF 43 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1998-479711 [41] WPIDS
DOC. NO. CPI: C1998-145121
TITLE: New bacteria strain Klebsiella **pneumoniae** GISK N 245 - shows complex of pathogenic factors, and can be used in **vaccine** production.
DERWENT CLASS: B04 D16
INVENTOR(S): GABIDULLIN, Z G; GASHIMOVA, D T; MAVZYUTOV, A R
PATENT ASSIGNEE(S): (UYBA-R) UNIV BASHKIR MED
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
RU 2105809	C1	19980227	(199841)*		3

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
RU 2105809	C1	RU 1995-121546	19951219

PRIORITY APPLN. INFO: RU 1995-121546 19951219
AB RU 2105809 C UPAB: 19981014
New bacteria strain Klebsiella **pneumoniae** GISK N 245, has complex of pathogenic factors.
USE - The new strain is useful in biotechnology, especially in production of thermolabile **enterotoxin** (**LT** -enterotoxin) and anatoxin of Klebsiella **pneumoniae**, suitable for use in preparation of **vaccines**.
ADVANTAGE - The new strain has increased toxin-production capability.
Dwg.0/0

L95 ANSWER 42 OF 43 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1997-108749 [10] WPIDS
DOC. NO. CPI: C1997-034688
TITLE: Treatment of auto-immune disease, prevention of T cell leukaemia, transplant rejection or graft versus host disease - by admin. of agent that binds to ganglioside GM1 or inhibits GM1-mediated signalling without binding.
DERWENT CLASS: B04 D16

INVENTOR(S): HIRST, T R; NASHAR, T O; WILLIAMS, N A; NASHAR, T
PATENT ASSIGNEE(S): (ORAT-N) ORATOL LTD; (UYBR-N) UNIV BRISTOL; (HIRS-I) HIRST T R; (NASH-I) NASHAR T O; (WILL-I) WILLIAMS N A
COUNTRY COUNT: 72
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9702045	A1	19970123	(199710)*	EN	63
RW: AT BE CH DE DK EA ES FI FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG					
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IL IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN					
AU 9663142	A	19970205	(199721)		
NO 9800005	A	19980305	(199820)		
EP 841939	A1	19980520	(199824)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE SI					
CZ 9800012	A3	19980617	(199830)		
HU 9900147	A2	19990528	(199930)		
JP 11508586	W	19990727	(199940)		61
MX 9800241	A1	19981101	(200022)		
KR 99028578	A	19990415	(200027)		
CN 1192693	A	19980909	(200040)		
AU 724516	B	20000921	(200050)		
NZ 311762	A	20010427	(200128)		
US 6287563	B1	20010911	(200154)		
US 2001036917	A1	20011101	(200168)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9702045	A1		WO 1996-GB1614	19960705
AU 9663142	A		AU 1996-63142	19960705
NO 9800005	A		WO 1996-GB1614	19960705
			NO 1998-5	19980102
EP 841939	A1		EP 1996-922162	19960705
			WO 1996-GB1614	19960705
CZ 9800012	A3		WO 1996-GB1614	19960705
			CZ 1998-12	19960705
HU 9900147	A2		WO 1996-GB1614	19960705
			HU 1999-147	19960705
JP 11508586	W		WO 1996-GB1614	19960705
			JP 1997-504927	19960705
MX 9800241	A1		MX 1998-241	19980107
KR 99028578	A		WO 1996-GB1614	19960705
			KR 1997-709899	19971230
CN 1192693	A		CN 1996-196258	19960705
AU 724516	B		AU 1996-63142	19960705
NZ 311762	A		NZ 1996-311762	19960705
			WO 1996-GB1614	19960705
US 6287563	B1		US 1997-999458	19971229
US 2001036917	A1	CIP of	US 1997-999458	19971229
			US 2001-867914	20010530

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9663142	A	Based on	WO 9702045

EP 841939	A1	Based on	WO 9702045
CZ 9800012	A3	Based on	WO 9702045
HU 9900147	A2	Based on	WO 9702045
JP 11508586	W	Based on	WO 9702045
KR 99028578	A	Based on	WO 9702045
AU 724516	B	Previous Publ.	AU 9663142
		Based on	WO 9702045
NZ 311762	A	Based on	WO 9702045

PRIORITY APPLN. INFO: GB 1995-13733 19950705
AB WO 9702045 A UPAB: 19970307
Method for treating or preventing autoimmune disease, human T-cell leukaemia, transplant rejection or graft versus host disease (GVHD) comprises admin. an agent (I) that:
(a) has **GM1 binding** activity or
(b) affects GM1-mediated intracellular signalling without binding to GM1.
Also claimed is the **vaccination** of mammals with (I), other than cholera toxin (Ctx) or E. coli heat-labile enterotoxin (Etx) admin. together with an unrelated foreign antigenic determinant (A).
USE - (I) shifts the immune response, to self or cross-reactive antigens, towards induction of Th2-associated cytokines, i.e. towards the self antigen and away from activation of inflammation. Specified diseases that can be treated are rheumatoid arthritis, multiple sclerosis and diabetes. When used against transplant rejection, the transplant may be allogenic or xenogeneic and GVHD following a bone marrow transplant. The **vaccination** method allows the immune response to be redirected, e.g. to favour a **mucosal** response. (I) are administered **mucosally**, e.g. as nasal spray or by injection.
Dwg.0/11

L95 ANSWER 43 OF 43 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 1989-339774 [46] WPIDS
DOC. NO. CPI: C1989-150589
TITLE: **Vaccine** derived from yersinia bacteria - to treat **hepatitis, herpes** and aids.
DERWENT CLASS: B04 D16
INVENTOR(S): CORNELIS, G
PATENT ASSIGNEE(S): (UYLO-N) UNIV CATHOLIQUE LOU
COUNTRY COUNT: 12
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 8910137	A	19891102	(198946)*	FR	
RW: AT BE CH DE FR GB IT LU NL SE					
W: JP US					
LU 87207	A	19891114	(198949)		13

PRIORITY APPLN. INFO: LU 1988-87207 19880429
AB WO 8910137 A UPAB: 19930923
Vaccine derived from Yersinia bacteria, in which at least one of the plasmid genes coding for an external membrane protein is replaced by at least one bacterial or viral gene coding for a protein or an epitope against which it is desired to **vaccinate**, is new.
The bacteria selected are pref. Y. enterocolitica or Y. pseudotuberculosis. The virulence of these bacteria is controlled by conventional means esp. by replacement of one or other protein coded by the plasmid, using an **immunogen**. The bacterial or viral genes

used to prepare the **vaccine** are pref. sub-unit B of toxin CT of Vibrio cholerae and of **enterotoxin LT** of E. coli, the surface antigen of the virus of **hepatitis** B (HBsAg) or the CS surface protein of Plasmodium falciparum.

USE/ADVANTAGE - The **vaccine** may be designed to combat, for example, **hepatitis** B, **herpes** simplex and AIDS. Yersinia bacteria have the useful properties of crossing the intestinal barrier without activating the immune system, carrying a large amt. proteins coded by plasmid pYV into the external membrane and even the culture medium, and possessing a system that allows the prodn. of these proteins in vivo, esp. when in contact with the immune system.
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